

## REMARKS

In response to the above-identified Final Office Action ("Action"), Applicants traverse the Examiner's rejection of the claims and seek reconsideration thereof. Claims 38, 42-57 and 60-66 are pending in the present application. Claims 38, 42-47 and 60-66 are rejected. In this response, no claims are amended, no claims are cancelled and claim 67 is added.

### **I. Claim Amendments**

Applicants respectfully submit herewith new claim 67. Support for claim 67 may be found, for example, on page 6, lines 20-26 and page 10, lines 20-30 of the Application. The amendments therefore are supported by the Application and do not add new matter.

### **II. Claim Rejections – 35 U.S.C. §103**

A. In the Action, claims 38 and 42-57 are rejected under 35 U.S.C. §103(a) as being unpatentable over International Publication No. WO 95/02069 issued to Bennett et al. ("Bennett") as evidenced by *The Use of Antisense Strategy to Modulate Human Melanogenesis* by Lazou et al. ("Lazou").

To establish a *prima facie* case of obviousness, the Examiner must set forth "some articulated reasoning with some rational underpinning to support the conclusion of obviousness." See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2007). In combining prior art elements to render the claimed combination of elements obvious, the Examiner must show that the results would have been predictable to one of ordinary skill in the art. See Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Section III(D), issued by the U.S. Patent and Trademark Office on October 10, 2007.

Applicants respectfully submit that for at least the following reasons, Bennett as evidenced by Lazou may not be relied upon to disclose or render predictable each and every element of independent claims 38 and 57.

#### ***Improper Rejection - Hindsight analysis***

In section 2142, MPEP clearly indicates that (underlining added):

*To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.*

However, in the present rejection, the Examiner clearly relies on impermissible hindsight.

Indeed, Lazou is a post-published article by the inventors of the present application describing results relevant for the present invention. As a result, the fact that the Examiner relies on this document in an obviousness rejection is unambiguously a proof of hindsight analysis.

The only reason that might authorize the Examiner to rely on such a document might be a rejection of inherent lack of novelty. However, the present rejection is on obviousness rejection, and Bennett is in any case not inherently novelty destroying (see below).

### ***Inherency***

In Office Action dated February 5, 2008, the Examiner rejected claims 38 and 42-57 for lack of novelty over the Bennett because of inherency.

However, this rejection has been withdrawn by the Examiner and should not be reiterated in an obviousness rejection. Nevertheless, the Examiner once more argues that Bennett inherently discloses the methods of claims 38 and 42-57 (see Office Action, page 9 lines 9-20).

Although this argument is not consistent with the obviousness rejection raised by the Examiner, Applicants wish to explain once more why Bennett does not inherently disclose the claimed methods.

Concerning inherency, MPEP in section 2112.IV clearly indicates:

*The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.*

MPEP further cites (underlining added), referring to *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981):

*"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "*

In the same paragraph, MPEP further states (underlining added):

*"[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004).*

In the present case, contrary to the assertions of the Examiner, Bennett does not explicitly or inherently disclose the topical application to the skin or hair of PKC beta 1 oligonucleotides.

Bennett relates to the use of antisense oligonucleotides targeting various PKC isoforms for inhibiting the corresponding PKC isoform and treating so-called PKC associated conditions.

In page 18, Bennett states (underlining added):

*"The pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the areas to be treated. Administration may be done topically (including ophthalmically, vaginally, rectally, intranasally), orally ... "*

This clearly indicates that topical application, which covers numerous administrations routes, skin or hair application not being explicitly recited, is contemplated only for diseases for which local topical application is current practice.

The only diseases recited in Bennett for which a topical application may be contemplated are skin cancer and psoriasis.

As mentioned in our previous responses, no association between skin cancer and PKC beta 1 is disclosed in Bennett. Bennett merely discloses that skin cancer might be treated by the administration (possibly topical) of an antisense oligonucleotide targeting one isoform of PKC among many others.

However, as clearly indicated by MPEP, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004). Therefore, it cannot be considered that Bennett discloses the topical application of anti-PKC beta 1 oligonucleotides for the treatment of skin cancer.

Concerning psoriasis, Bennett only mentions in page 4 (underlining added):

*"For example, in psoriatic lesions there is an alteration in the ratio between PKC- $\alpha$  and PKC- $\beta$ , with preferential loss of PKC- $\beta$  compared to normal skin."*

This clearly indicates that psoriasis is associated with a decrease of PKB beta (without any detail concerning which of PKC beta 1 and/or 2 is involved), a treatment necessarily involving a stimulation of PKC beta expression. However, since the invention of Bennett relies on antisense oligonucleotides, which are known to inhibit the expression of their target, it is clear that antisense oligonucleotides targeting PKC beta 1 are not useful, and could even be harmful,

for the treatment of psoriasis. Therefore, it clearly cannot be considered that Bennett discloses the topical application of anti-PKC beta 1 oligonucleotides for the treatment of psoriasis.

Indeed, MPEP in section 2141.02- VI states (underlining added):

*A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. WL. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)*

In the present case, the fact that psoriasis is said to be associated to a decrease in PKC beta expression clearly teaches away from using antisense oligonucleotides targeting PKC beta 1 for the treatment of psoriasis.

In summary, Bennett broadly speculates on the possibility to treat various diseases, by various administration routes, using any of many antisense oligonucleotides targeting various PKC isoforms, and thus represents a mere invitation to conduct further research in order to determine which particular isoform is relevant for which disease, and which is the best administration mode.

As a result, based on MPEP section 2112.IV, it is clear that Bennett does not disclose, neither explicitly nor inherently, the topical application of antisense oligonucleotides targeting PKC beta 1, and thus does not disclose, neither explicitly nor inherently, a depigmenting effect of antisense oligonucleotides targeting PKC beta 1.

### ***Non obviousness***

Excepting the disclosure of antisense oligonucleotides specifically targeting PKC beta 1, Bennett does not provide any other teaching relating to PKC beta 1 isoform.

As a result, the only teaching that may be derived from Bennett is that antisense oligonucleotides specifically targeting PKC beta 1 may be used in the treatment of a condition involving PKC beta 1 overexpression. This is clearly not sufficient to make claims 38 and 42-57 obvious over Bennett.

While this document is not mentioned in the rejection title, the Examiner also refers to Park et al, 1993 ("Park"), which would allegedly provide a motivation or evidence of the level of skill in the art for using antisense oligonucleotides specifically targeting PKC beta 1 for depigmentation purposes.

Park describes the analysis of non pigmented melanocytes (NP-MM4 cells), either as such, or after transfection with a cDNA encoding PKC beta (see Materials and Methods, page 11743, § entitled "Transient transfections"). The authors show that, while NP-MM4 cells are normally not pigmented, their transfection with a cDNA encoding PKC beta results in restoration of pigmentation, thus involving PKC beta expression in melanogenesis.

However, the Examiner totally omits the fact that Park does not refer to PKC beta 1, but to PKC beta, which includes both PKC beta isoforms 1 and 2.

At the date of publication of the article by Park, it was already well known in the art that PKC beta was made of two isoforms (PKC beta 1 and 2), differing in their C- terminal amino acid sequence, as demonstrated by the article attached herewith titled *Primary structures of human protein Kinase C  $\beta$ I and  $\beta$ II differ only in their C-terminal sequences* (1987) by Kyoko Kubo et al. In this respect, Applicants respectfully draw the attention of the Examiner to the fact that one of the authors of Park is also one of the authors of Kyoko Kubo et al.

Since PKC beta was known to cover two isoforms, the use of the general term "PKC beta" would clearly have been understood by one of ordinary skill in the art as including both isoforms.

One of ordinary skill in the art would thus derive from Park that both PKC beta 1 and 2 are necessary for pigmentation, and that depigmentation would necessitate the inhibition of both PKC beta 1 and 2.

By combining the teachings of Bennett and Park, one of ordinary skill in the art might have used oligonucleotides targeting both PKC beta 1 and 2 (see Bennett, Table 2, page 26) and would thus have arrived to another result than the present invention.

However, the present application, as well as the article by Lazou, surprisingly demonstrate that, contrary to the suggestions of Park, the inhibition of PKC beta 1 only is sufficient to inhibit melanogenesis and thus obtain depigmentation.

In addition, the inhibition of PKC beta 1 only instead of both PKC beta 1 and 2 is highly advantageous. Indeed, as indicated in Lazou (see page s2, right column), the inventors found that in human skin, PKC beta 1 expression is restricted to melanocytes. This ensures that inhibition of PKC beta 1 does not also inhibit other essential functions in the skin.

In contrast, PKC beta 2 is also expressed in Langerhans cells (see article enclosed herewith title *Protein Kinase C  $\beta$ II Plays an Essential Role in Dendritic Cell Differentiation and Autoregulates Its Own Expression* (2005) by Cejas et al), a particular type of dendritic cell located in the skin (see enclosed herewith an article on Langerhans cells from Wikipedia.com), which play the essential role of immune sentinels in the skin. Moreover, Cejas et al demonstrate that PKC beta 2 plays a crucial role in the differentiation of Langerhans cells.

As a result, by following the combined teachings of Bennett and Park, one of ordinary skill in the art would have arrived to the use of antisense oligonucleotides targeting both PKC beta 1 and 2, which would permit depigmentation but would also hamper essential functions of the skin.

In contrast, the methods according to the invention advantageously permit to obtain depigmentation, without adversely altering other essential skin functions, since the expression of PKC beta 1 is restricted in the skin to melanocytes.

In summary, the combined teachings of Bennett and Park lead to another result than the present invention, which result is surprisingly and clearly disadvantageous compared to the present invention.

Thus, for at least the foregoing reasons, claims 38 and 57 are not obvious in view of the cited prior art. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 38 and 57 under 35 U.S.C. §103.

In regard to claims 42-56, these claims depend from claim 38 and incorporate the limitations thereof. Thus, for at least the reasons that claim 38 is not *prima facie* obvious in view of the cited prior art, claims 42-56 are further not obvious over the cited prior art references. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42-56 under 35 U.S.C. §103.

**B.** In the Action, claims 60-66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Bennett as evidenced by *The Beta Isoform of Protein Kinase C Stimulates Human Melanogenesis by Activating Tyrosinase in Pigment Cells* by Park et al. ("Park").

Claims 60-66 depend from claim 38 and incorporate the limitations thereof. While the Examiner this time properly refers to Bennett and to the article by Park, the same reasoning as presented above with regard to claim 38 clearly shows that claims 60-66 are also not obvious over Bennett and Park. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 60-66 under 35 U.S.C. §103 over Bennett as evidenced by Park.

### **III. Claim 67**

New claim 67 depends from claim 38 and incorporate the limitations thereof. Thus, for at least the reasons that claim 38 is not obvious in view of the cited prior art references, claim 67 is further patentable over the art of record. Applicants respectfully submit that the cited prior art references further fail to disclose the element of "wherein the topical application of the composition to the skin results in depigmentation by modifying the expression of only PKC beta 1" as recited in claim 67. As previously discussed, the teachings of Bennett and Park, may have led one of ordinary skill in the art to use oligonucleotides targeting both PKC beta 1 and 2 (see Bennett, Table 2, page 26), not PKC beta 1 alone to achieve depigmentation as required by claim 67. Applicants respectfully request consideration and allowance of claim 67 at the Examiner's earliest convenience.



### CONCLUSION

In view of the foregoing, it is believed that all claims now pending are in condition for allowance and such action is earnestly solicited at the earliest possible date. If there are any additional fees due in connection with the filing of this response, please charge those fees to our Deposit Account No. 02-2666. Questions regarding this matter should be directed to the undersigned at (310) 207-3800.

### PETITION FOR EXTENSION OF TIME

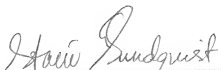
Per 37 C.F.R. 1.136(a) and in connection with the Office Action mailed on November 18, 2009, Applicants respectfully petition Commissioner for a three (3) month extension of time, extending the period for response to May 18, 2010. The amount of \$1,110.00 to cover the petition filing fee for a 37 C.F.R. 1.17(a)(3) large entity will be charged to our Deposit Account No. 02-2666.

Respectfully submitted,

BLAKELY, SOKOLOFF, TAYLOR, & ZAFMAN LLP

Dated: May 18, 2010

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### CERTIFICATE OF TRANSMISSION

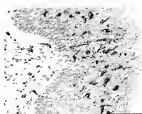
I hereby certify that this correspondence is being submitted electronically via EFS Web to the United States Patent and Trademark Office on May 18, 2010.

\_\_\_\_\_  
Suzanne Johnston

# Langerhans cell

From Wikipedia, the free encyclopedia

**Langerhans cells** are dendritic cells<sup>[2]</sup> in the epidermis,<sup>[3]</sup> containing large granules called Birbeck granules. They are normally present in lymph nodes and other organs, including the stratum spinosum layer of the epidermis. They can be found elsewhere, particularly in association with the condition histiocytosis.



Section of skin showing large numbers of dendritic (Langerhans cells) in the epidermis. (*M. ulcerans* infection, S100 immunoperoxidase stain.)

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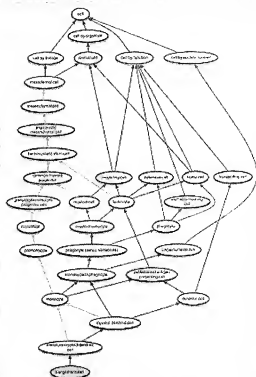
## History

The Langerhans cell is named after Paul Langerhans, a German physician and anatomist, who discovered the cells at the age of 21 while he was a medical student.<sup>[4]</sup> He mistakenly identified the cells as part of the nervous system.<sup>[5]</sup>

## Function

On infection of an area of skin, the local Langerhans cells will take up and process microbial antigens to become fully-functional antigen-presenting cells.

Generally, dendritic cells in tissue are active in the capture, uptake and processing of antigens. Once dendritic cells arrive in secondary lymphoid tissue, however, they lose these properties while gaining the capacity to interact with naive T-cells.



The representation of Langerhans cells in the Cell Ontology. A portion of the Cell Ontology is shown with ovals corresponding to cell types defined in the ontology and arrows corresponding to relations between those cell types. From Masci et al., 2009.<sup>[1]</sup>

Langerhans cells are derived from the cellular differentiation of monocytes with the marker "Gr-1" (also known as "Ly-6G/Ly-6C"). The differentiation requires stimulation by colony stimulating factor (CSF)-1.<sup>[6]</sup> They are similar in morphology and function to macrophages.<sup>[7]</sup>

Langerin is a protein found in Langerhans cells,<sup>[8]</sup> and other types of dendritic cells.<sup>[9]</sup>

## Clinical significance

### LCH

In the rare disease Langerhans cell histiocytosis (LCH), an excess of these cells is produced, which can cause damage to skin, bone and other organs.

### HIV

Langerhans cells capture HIV-1 virions by way of Fc receptor binding to antibody-coated virus. Langerhans cells act as reservoirs for the HIV-1 virus, serving as a site of replication when T-cells become depleted (Robbins Pathology).

Langerhans cells have been observed in foreskin, vaginal, and oral mucosa of humans; the lower concentrations in oral mucosa suggest that it is not a likely source of HIV infection relative to foreskin and vaginal mucosa.<sup>[10]</sup>

On March 4, 2007 the online Nature Medicine magazine published the letter "Langerin is a natural barrier to HIV-1 transmission by Langerhans cells."<sup>[11]</sup> Teunis Geijtenbeek, one of the authors of the study, said that "Langerin is able to scavenge viruses from the surrounding environment, thereby preventing infection" and "since generally all tissues on the outside of our bodies have Langerhans cells, we think that the human body is equipped with an antiviral defense mechanism, destroying incoming viruses."<sup>[12]</sup>

## See also

- Langhans giant cell

## References

- ↑ Masci AM, Arighi CN, Diehl AD, Lieberman AE, Mungall C, Scheuermann RH, Smith B, Cowell LG (2009). "An improved ontological representation of dendritic cells as a paradigm for all cell types (<http://www.biomedcentral.com/1471-2105/10/70>) ". *BMC Bioinformatics* **10**: 70. doi:10.1186/1471-2105-10-70 (<http://dx.doi.org/10.1186/2F1471-2105-10-70>) . PMID 19243617 (<http://www.ncbi.nlm.nih.gov/pubmed/19243617>) . PMC 2662812 (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2662812>) . <http://www.biomedcentral.com/1471-2105/10/70>.
- ↑ Musso T, Scutera S, Vermi W, *et al.* (2008). "Activin A induces Langerhans cell differentiation in vitro and in human skin explants (<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0003271>) ". *PLoS ONE* **3** (9): e3271. doi:10.1371/journal.pone.0003271 (<http://dx.doi.org/10.1371/2Fjournal.pone.0003271>) . PMID 18813341 (<http://www.ncbi.nlm.nih.gov/pubmed/18813341>) . PMC 2533393 (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2533393>) . <http://www.plosone.org/article/info:doi/10.1371/journal.pone.0003271>.
- ↑ Merad M, Ginhoux F, Collin M (December 2008). "Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells". *Nat. Rev. Immunol.* **8** (12): 935–47. doi:10.1038/nri2455 (<http://dx.doi.org/10.1038/2Fnr2455>) . PMID 19029989 (<http://www.ncbi.nlm.nih.gov/pubmed/19029989>) .

4. ^ Langerhans, P (1868). "Ueber die Nervender menschlicher" (in German). *Haut. Virchows Arch. (Pathol. Anat.)* 44: 325. doi:10.1007/BF01959006 (<http://dx.doi.org/10.1007%2FBF01959006>) .
5. ^ Online 'Mendelian Inheritance in Man' (OMIM) Langerhans cell histiocytosis -604856 (<http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=604856>)
6. ^ Ginhoux F, Tacke F, Angeli V, Bogunovic M, Loubreau M, Dai X, Stanley E, Randolph G, Merad M (2006). "Langerhans cells arise from monocytes in vivo". *Nat Immunol* 7 (3): 265–73. doi:10.1038/ni1307 (<http://dx.doi.org/10.1038%2Fni1307>) . PMID 16444257 (<http://www.ncbi.nlm.nih.gov/pubmed/16444257>) .
7. ^ Semester 4 medical lectures at Uppsala University 2008 by Leif Jansson
8. ^ Valladeau J, Dezutter-Dambuyant C, Sacland S (2003). "Langerin/CD207 sheds light on formation of birbeck granules and their possible function in Langerhans cells". *Immunol. Res.* 28 (2): 93–107. doi:10.1385/IR.28.2.93 (<http://dx.doi.org/10.1385%2FIR.28.2.93>) . PMID 14610287 (<http://www.ncbi.nlm.nih.gov/pubmed/14610287>) .
9. ^ Poulin LF, Henri S, de Bovis B, Devillard E, Kissenpfennig A, Malissen B (December 2007). "The dermis contains langerin+ dendritic cells that develop and function independently of epidermal Langerhans cells (<http://www.jem.org/cgi/pmidlookup?view=long&pmid=18086861>)". *J. Exp. Med.* 204 (13): 3119–31. doi:10.1084/jem.20071724 (<http://dx.doi.org/10.1084%2Fjem.20071724>) . PMID 18086861 (<http://www.ncbi.nlm.nih.gov/pubmed/18086861>) . PMC 2150992 (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=2150992>) . <http://www.jem.org/cgi/pmidlookup?view=long&pmid=18086861>.
10. ^ Hussain, LA, Lehner T (1995). "Comparative Investigation of Langerhans' cells and Potential Receptors for HIV in Oral, Genitourinary and Rectal Epithelia". *Immunology* 85: 475–484. PMID 7558138 (<http://www.ncbi.nlm.nih.gov/pubmed/7558138>) .
11. ^ de Witte L, Nabatov A, Pion M, Fluitsma D, de Jong M, de Grijp T, Piguët V, van Kooyk Y, Geijtenbeek T (2007). "Langerin is a natural barrier to HIV-1 transmission by Langerhans cells". *Nat Med* 13 (3): 367–71. doi:10.1038/nm1541 (<http://dx.doi.org/10.1038%2Fnm1541>) . PMID 17334373 (<http://www.ncbi.nlm.nih.gov/pubmed/17334373>) .
12. ^ Mundell, E.J. (March 5, 2007). "Scientists Discover 'Natural Barrier' to HIV (<http://sexualhealth.e-healthsource.com/index.php?p=news1&id=602421>)". HealthDay News via sexualhealth.e-healthsource.com. <http://sexualhealth.e-healthsource.com/index.php?p=news1&id=602421>. Retrieved 2008-07-13.

## External links

- *Langerhans Cell Histiocytosis* (<http://www.emedicine.com/derm/topic216.htm#>) at eMedicine
- Illustration at trinity.edu (<http://www.trinity.edu/rblyston/MicroA/Lectures/L34-html/img018.jpg>)
- Birbeck granules at djo.harvard.edu ([http://www.djo.harvard.edu/site.php?url=/physicians/gr356&page=GR\\_AG](http://www.djo.harvard.edu/site.php?url=/physicians/gr356&page=GR_AG))
- MeSH *Langerhans + Cells* ([http://www.nlm.nih.gov/cgi/mesh/2009/MB\\_cgi?mode=&term=Langerhans+Cells](http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Langerhans+Cells))

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Categories: Mononuclear phagocytes | Skin anatomy

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